CPMA

COLOR PIGMENTS MANUFACTURERS ASSOCIATION, INC.

201-14995

December 29, 2003

Mr. Mike Leavitt
Administrator
U.S. Environmental Protection Agency
PO Box 1473
Merrifield, VA 22116
Attention: Chemical Right-to Know Program

Re: Submission of Test Plans Pursuant to the High Production Volume Testing Program for Diketene Chemical Abstracts Service ("CAS") No. 674-82-8 Methyl Acetoacetate CAS No.105-45-3, and N,N-Dimethylacetoacetamide ("DMAA"), CAS No. 2044-64-6.

Dear Mr. Leavitt:

I am writing on behalf of the Color Pigments Manufacturers Association, Inc. ("CPMA"). The CPMA is an industry trade association representing color pigment companies in Canada, Mexico, and the United States. CPMA represents small, medium, and large color pigments manufacturers throughout Canada, Mexico and United States, accounting for approximately 95% of the production of color pigments in North America. Color Pigments are widely used in product compositions of all kinds, including paints, inks, plastics, glass, synthetic fibers and ceramics. Color pigment manufacturers located in other countries with sales in Canada, Mexico, and the United States, and suppliers of intermediates to the pigments industry are also members of the Association.

With this letter, we are submitting the enclosed Test Plans for the compounds Diketene, Chemical Abstracts Service ("CAS") No. 674-82-8, and Methyl Acetoacetate ("MAA"), CAS No.105-45-3, and N,N-Dimethylacetoacetamide ("DMAA"), CAS No. 2044-64-6.

The sponsoring companies for these Test Plans are:

Lonza Corporation
Eastman Chemical Corporation

Representatives of these two companies make up the Diketene Dirivatives Task Force within the CPMA. As discussed in our letter of November 30, 1999:

> "CPMA reserves the right to defer review of any chemical under the HPV program where that chemical has been the subject of another commitment to either the EPA-HPV program or other similar programs. CPMA further reserves the right to withdraw from this commitment should the HPV program, when and if finalized, prove to be different from that currently understood by CPMA."

300 North Washington Street, Suite 102 • Alexandria, Virginia 22314 • (703) 684-4044 • FAX: (703) 684-1795
Mailing Address: P.O. Box 20839 • Alexandria, Virginia 22320-1839 • e-mail: cpma@cpma.com

Furthermore, and again as discussed in our letter of November 30, 1999, the CPMA is taking steps to review and categorize the available data for the chemicals sponsored by the CPMA. This effort has required, and will continue to require, considerable time, since many of these products have been produced for over 50 years throughout the world. Additionally, an increasing number of the substances sponsored by the CPMA have become the subject of international efforts under the Organization for Economic Cooperation and Development SIDS program. All testing for such chemicals and structural analogs will be deferred until such time as international SIDS reports are complete.

Therefore, the submission of the enclosed test plans for DMAA, MAA and Diketene does not in any way modify CPMA's previously stated reservations or stated positions with respect to the voluntary HPV program.

All technical questions should be addressed to me at:

Color Pigments Manufacturers Associations, Inc.
Attn: J. Lawrence Robinson, President
Suite 102
300 North Washington Street
Alexandria, Virginia 22314

Telephone: 703/684-4044
Facsimile: 703/684-1795

I will, in turn, forward requests to the appropriate member representatives for review and response. Thank you for your attention in this matter. Please call if there are any questions or comments.

Sincerely,

J. Lawrence Robinson
President

Enclosures

201-14995

HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN FOR

2-OXETANONE, 4-METHYLENE

"DIKETENE"

CAS NO.: 674-82-8

PREPARED BY:
COLOR PIGMENTS MANUFACTURERS ASSOCIATION, INC.
DIKETENE DERIVATIVES TASK FORCE

December 29, 2003

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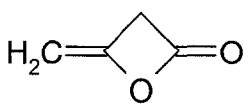
OVERVIEW

The Diketene Derivatives Task Force (DDTF) of the Color Pigments Manufacturers Association (CPMA) and its member companies hereby submit for review and public comment the test plan for 2-oxetanone, 4-methylene (diketene; CAS No.: 674-82-8) under the U. S. Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of the DDTF and its member companies to use either existing data on diketene or data that will be generated in the future under the ICCA HPV program, predictive computer models, or data from structurally similar compounds to adequately fulfill the Screening Information Data Set (SIDS) for physical-chemical properties, environmental fate, ecotoxicity, and toxicological and human health effects. The DDTF believes that these data, in total, will fulfill all the requirements of the US HPV program without need for the conduct of any additional tests by the DDTF.

TEST PLAN SUMMARY

CAS No. 674-82-8 	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	Y	-	N	Y	N
Partition Coefficient	Y	-	-	Y	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	-	Y	-	N	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	N	Y	-	N	N	N
Acute Toxicity to Aquatic Invertebrates	N	-	-	-	-	N	N
Toxicity to Aquatic Plants	N	-	-	-	-	N	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	N	Y	-	N	Y	N
Repeated Dose Toxicity[1]	N	-	-	-	-	-	N
Genetic Toxicity – Mutation[1]	N	-	-	-	-	-	N
Genetic Toxicity – Chromosomal Aberrations[1]	N	-	-	-	-	-	N
Developmental Toxicity[1]	N	-	-	-	-	-	N
Toxicity to Reproduction[1]	N	-	-	-	-	-	N

1. Endpoint is completed through the use of data from the chemical surrogates' ethyl acetoacetate and methyl acetoacetate.

TEST PLAN FOR DIKETENE

I. Background

Diketene is a clear colorless liquid of very high purity. Diketene is used as a chemical intermediate in the production of acetoacetate esters and acetoacetanilides, dyes, color pigments, pharmaceuticals, food preservatives and insecticides. It is a very chemically unstable substance that rapidly degrades upon contact with water to form acetoacetic acid (diacetic acid). Diacetic acid is capable of undergoing further decomposition or can be metabolized in mammalian systems to form acetone and CO_2, diketene also readily reacts with oxidizing materials and is capable of undergoing extremely dangerous polymerization reactions if not properly handled. It is manufactured and transported in closed-systems and sold to a limited number of customers who also handle this material in closed systems. There is no known direct or consumer use of the chemical where exposure to the general population may occur. Exposure to diketene by employees is minimized by its manufacture, transport, and use in closed-systems as well as the use of good industrial hygiene practices. Exposure is also self-limited by the fact that this chemical is known to be extremely irritating to the eyes and mucous membranes of the respiratory tract. Exposure to the environment is unlikely except under conditions of an accidental release during manufacture or transport.

It is also important to point out that this chemical has been sponsored by Wacker-Chemie GmbH as part of the ICCA HPV initiative (See ICCA HPV website). Accordingly, as part of that program SIDS dossier and a SIDS screening information assessment report (SIAR) and a SIDS initial assessment profile (SIAP) will be prepared that will cover the same endpoints of concern required in the US EPA's HPV program. As such, the DDTF does not want to initiate any testing that may be duplicative of test that may have already been completed by Wacker-Chemie GmbH to fulfill its obligation under the ICCA program.

II. Justification for the Use of Data from Surrogate Chemicals

As a means to reduce the number of tests that may be conducted, the EPA allows for the use of categories to group together chemicals that are structurally similar to characterize specific SIDS endpoints (USEPA 1999a). At this time the only data that exist to assess toxicity in mammalian systems is acute toxicity data. Accordingly, the DDTF believes that the endpoints assessing genotoxicity, repeated exposure toxicity and developmental and reproductive toxicity hazards can be evaluated through the use of structural surrogates.

As noted above, diketene is an extremely unstable molecule that is well known to rapidly degrade upon contact with water to form acetoacetic acid (AAA; CAS No.: 541-50-4). AAA is a compound that is endogenously produced in the body as part of normal metabolism of lipids where it undergoes further decomposition to form acetone and CO_2. In addition, the compounds ethyl acetoacetate (EAA; CAS No.: 141-97-9) and methyl acetoacetate (MAA; CAS No.: 105-45-3) which are compounds formed by ester linkages between AAA and the respective alcohols, ethanol and methanol, are also fully anticipated to be metabolized by esterase activity in biological systems to yield AAA and the respective alcohols. EAA is in the ICCA HPV program and was recently reviewed at SIAM 12 where it was concluded to be a chemical of low risks to both the environment and to human health. This was based on a robust set of data covering all SIDS endpoints (See OECD website for published SIAP). The complete data set for this compound should be available to the public through the EPA. MAA is in the US EPA HPV program and, similar to EAA, has a complete SIDS database available to the public.

Thus, it is the conclusion of the DDTF that due to the rapid degradation and or metabolism of diketene to AAA upon contact with water and based on the strong assumption that the metabolism of MAA and EAA will also yield AAA (actual metabolism data for EAA and MAA are not available) the hazard assessment of diketene for all end points beyond acute exposure can be deduced from the information available on MAA and EAA.

III. Description of the Test Plan for Each SIDS Endpoint

A. Physical –Chemical Data

Melting point –	Values for this endpoint were obtained from reputable textbooks.
Boiling point -	Values for this endpoint were obtained from reputable textbooks.
Vapor pressure -	Values for this endpoint were obtained from reputable textbooks.
Partition coefficient -	A value for this endpoint was obtained using KOWIN (v1.67), a computer estimation program (1).
Water solubility -	Values for this endpoint were obtained from a reputable textbook and using WSKOW (v1.41), a computer estimation program(1)
Conclusion:	All endpoints are satisfied by, either actual data found within reputable textbooks or from acceptable estimation models. These data are of sufficient quality to conclude that no additional testing is required.

B. Environmental Fate Endpoints

Photodegradation -	A value for this endpoint was obtained using AOPWIN (v1.91), a computer estimation program (1).
Stability in Water -	A value for this endpoint was obtained from two studies. The first was a measure of the kinetic heat of reaction of hydrolysis showing the reaction to be exothermic. The second study involved the automatic recording titration, which was used to determine the hydrolysis rate constant.
Biodegradation -	This endpoint was satisfied through the use of existing data from a multi-day ready biodegradability assessment using a Modified MITI Test (I) OECD TG-301C.
Transport between Environ. Compartments (Fugacity) -	Transport between environmental compartments was determined using EPIWIN:EQC, a Level III Fugacity computer modeling system(1).
Conclusion:	All endpoints have been satisfied using data or estimation models that are of sufficient quality to conclude that no additional testing is necessary. The principle use of this substance is a chemical intermediate and because the substance is manufactured and handled in closed-systems it is highly unlikely to enter into the environment.

C. Ecotoxicity Data

Acute Toxicity to Fish -	This endpoint contains data from a single acute toxicity study in Golden Orfe. However, the reliability of this study is of questionable validity. A prediction of the acute toxicity of AAA using the ECOSAR estimation program within EPIWIN indicates the material to be of very low toxicity potential.

Acute Toxicity to Aquatic Invertebrates - No data are available for this end point. A prediction of the acute toxicity of AAA using the ECOSAR estimation program within EPIWIN indicates the material to be of very low toxicity potential.

Toxicity to Aquatic Plants - No data are available for this end point. A prediction of the acute toxicity of AAA using the ECOSAR estimation program within EPIWIN indicates the material to be of very low toxicity potential.

Conclusion: Diketene is a highly reactive, unstable chemical substance. In presence of water it rapidly hydrolyzes to produce AAA. The AAA further decomposes to acetone and carbon dioxide. The principle use of this substance is a chemical intermediate and because the substance is manufactured and handled in closed-systems it is highly unlikely to enter into the environment. The testing of diketene in aquatic environments would be of questionable value due to its inherent instability. However, since the results of ECOSAR estimation programs indicate the diketene degradation product AAA to be of such low toxicity and due to the fact that Wacker-Chemie GmbH has accepted the ICCA HPV Initiative to prepare a SIDS Dossier for diketene, the DDTF does not want to initiate any testing that may be duplicative of test that may have already been completed by Wacker-Chemie GmbH to fulfill its obligation under the ICCA program that are not available to the DDTF.

C. Toxicity Data

Acute Toxicity - This endpoint was fulfilled by data from several studies following oral, dermal, and inhalation exposure. All studies were conducted prior to establishment of the OECD Test Guidelines and GLP testing requirements. They are nevertheless of sufficient quality to conclude that no new testing is needed.

Repeated Dose Toxicity - No data on diketene are available for this end point. Thus, this endpoint was fulfilled by data from the chemical surrogates MAA and EAA. In addition, data from three carcinogenicity studies conducted under National Cancer Institute sponsorship and guidelines have been briefly summarized.

Genetic Toxicity Mutation - No data on diketene are available for this end point. The purpose of these *in vitro* studies is as a predictor for *in vivo* carcinogenicity. Based upon the absence of such an effect in the three carcinogenicity studies it would appear that such data would be of limited value. In addition, data from the chemical surrogates MAA and EAA can be utilized to complete this endpoint.

Genetic Toxicity Chromosomal Aberration - No data on diketene are available for this end point. The purpose of these *in vitro* studies is as a predictor for *in vivo* carcinogenicity. Based upon the absence of such an effect in the three carcinogenicity studies it would appear that such data would be of limited value. In addition, data from the chemical surrogates MAA and EAA can be utilized to complete this endpoint.

Developmental Toxicity - No data on diketene are available for this end point. Thus, this endpoint was fulfilled by data from the chemical surrogates MAA and EAA. In addition, the rapid hydrolysis rate and chemical reactivity of diketene in

aqueous environments would result in its decomposition to AAA before it reached the placental membrane or the conceptus.

Reproductive Toxicity - No data on diketene are available for this end point. Thus, this endpoint was fulfilled by data from the chemical surrogates MAA and EAA. In addition, the rapid hydrolysis rate and chemical reactivity of diketene in aqueous environments would result in its decomposition to AAA before it reaches reproductive organs.

Conclusion: Diketene is a highly reactive, unstable chemical substance that presents very real hazards if improperly handled making the shipping and testing of this molecule extremely difficult. In presence of water it rapidly hydrolyzes to produce AAA which is known to be metabolized to acetone and carbon dioxide. The principle use of this substance is a chemical intermediate and because the substance is manufactured and handled in closed-systems exposure to humans is unlikely. Since complete SIDS datasets have been developed on MAA and EAA which are strongly believed to be metabolized to AAA, the DDTF believe no further toxicity testing of diketene are believed to be warranted. Furthermore, no additional testing is proposed, as Wacker-Chemie GmbH has accepted the ICCA HPV initiative to prepare a SIDS dossier for diketene and the DDTF does not want to conduct any tests which may be duplicative.

IV. Evaluation of Data for Quality and Acceptability

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch *et al.* (4). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicity and human health endpoints per US EPA recommendations (3). The codification described by Klimisch *et al.* (4) specifies four categories of reliability for describing data adequacy.

These are:

(1) Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) assurances or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or were insufficiently documented.

(4) Not assignable: Includes studies or data in which insufficient detail to assign a rating, *e.g.*, listed in abstracts or secondary literature.

References

1. EPI™ Suite. Version 3.11. U.S. Environmental Protection Agency, Washington, DC 20460.

2. US EPA. 1999a. The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

3. USEPA, 1999b, Determining the Adequacy of Existing of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/1999.

4. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol. 25:*1-5.

201-14995

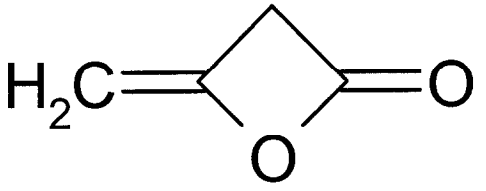
I. General Information

CAS Number: 674-82-8

Name: 4-Methylene-2-oxetanone
Acetyl ketene
Diketene
But-3-en-3-olide

Formula : $C_4H_4O_2$

Structure:



II. Physical-Chemical Data

A. Melting Point

Test Substance	
Test Substance:	Diketene
Remarks:	Purity: Not specified
Method	
Method:	Not specified
GLP:	Unknown
Year:	1979
Results	
Melting Point value:	- 6.5°C
Reference	Sax, N.I., Dangerous Properties of Industrial Materials, 5th ed., New York, Van Nostran Rhienhold, 1979.
Test Substance	
Test Substance:	Diketene
Remarks:	Purity: Not specified
Method	
Method:	Not specified
GLP:	Unknown
Year:	1990
Results	
Melting Point value:	- 7.5°C
Reference	Elvers, B. et al, ed., Ullmann's Encyclopedia of Industrial Chemistry, Completely Revised 5th ed., New York, VCH Publishers, 1990.

B. Boiling Point

Test Substance	
Test Substance:	Diketene
Remarks:	Purity: Not specified
Method	
Method:	Not specified
GLP:	Unknown
Year:	1994
Results	
Boiling Point value:	127.4 °C
Reference	Sax, N.I., Dangerous Properties of Industrial Materials, 8th ed., New York, Van Nostran Rhienhold, 1994.
Test Substance	
Test Substance:	Diketene
Remarks:	Purity: Not specified
Method	
Method:	Not specified
GLP:	Unknown
Year:	1990
Remarks:	
Results	
Boiling Point value:	127.4 °C
Pressure with units:	101.3 kPa
Decomposition:	350 – 600 °C
Remarks:	
Reference	Elvers, B. et al, ed., Ullmann's Encyclopedia of Industrial Chemistry, Completely Revised 5th ed., New York, VCH Publishers, 1990.

C. Vapor Pressure

Test Substance	
Test Substance:	Diketene
Remarks:	Purity: Not specified
Method	
Method:	Not specified
GLP:	Unknown
Year:	1989
Results	
Vapor pressure value:	10.7 mm Hg
Temperatures:	25 °C
Reference	Daubert, T.E. & R.P. Danner, Physical and Thermodynamic Properties of Pure Chemicals: Data Compilation, Design institute for Physical Properties Data, Amer. Inst. Chem. Eng., Hemisphere Pub. Corp., New York, NY, 4 Vol., 1989.

Test Substance	
Test Substance:	Diketene
Remarks:	Purity: Not specified
Method	
Method:	Not specified
GLP:	Unknown
Year:	1990
Results	
Vapor pressure value:	1.07 kPa
Temperatures:	20 °C
Reference	Elvers, B. et al, ed., Ullmann's,encyclopedia of Industrial Chemistry, Completely Revised 5th ed., New York, VCH Publishers, 1990.

D. Partition Coefficient

Test Substance	
Test Substance:	Diketene
Method	
Method:	Estimation
Results	
Log P_{ow}:	
Remarks:	- 0.39
Reference	KOWIN (v1.67); EPI SUITE™ (v3.11) Meylan, W.M. and P.H. Howard. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. *J. Pharm. Sci.* **84**:83-92.

E. Water Solubility

Test Substance	
Test Substance:	Diketene
Method	
Method:	Estimation
Results	
Value:	5.30 E+005 mg/l (530 g/l)
Temperature:	25°C
Reference	WSKOWWIN (v1.41); EPI SUITE™ (v3.11) Meylan, W.M., P.H. Howard, R.S. Boethling. 1996. Improved method for estimating water solubility from octanol/water partition coefficient. *Environ. Toxicol. Chem.* **15**:100-106.

Test Substance	
Test Substance:	Diketene
Remarks:	Purity unknown
Method	
Method:	Unknown
Results	
Value:	Soluble
Remarks:	Decomposes in water
Reference	Sax, N.I., Dangerous Properties of Industrial Materials, 8th ed., New York, Van Nostran Rhienhold, 1994.

III. Environmental Fate Endpoint

A. Photodegradation

Test Substance	
Test Substance:	Diketene
Remarks:	
Method	
Method:	Estimation
Test type:	Atmospheric Oxidation
Results	
Temperature:	25 °C
Hydroxyl radical reaction	
OH Rate constant:	5.15 x 10E-11 cm^3/molecule-sec
Half-life:	0.208 days (12-hr/day; 1.5 x 10E6 OH/cm^3)
Ozone reaction:	
Ozone Rate constant:	1.14 x 10E-17 cm^3/molecule-sec
Half-life:	1.0 days at 7 x 10E11 O_3/cm^3
Remarks:	Estimated value based upon acceptable model
Conclusions	Material is oxidized by atmospheric hydroxyl radicals at a rapid rate and by Ozone at a moderate rate.
Reference	AOPWIN (v1.91); EPI SUITE™ (v3.11); Meylan, W.M. and P.H. Howard (1993), Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone. *Chemosphere* **26**:2293-2299.

B. Stability in Water

Test Substance	
Test Substance:	Diketene
Remarks:	Purity unknown
Method	
Method:	Experimental
Test type:	Kinetic measurement – Heat of Reaction
GLP:	Unknown
Year:	1992
Results	
Nominal value:	$\Delta_r H° = -118.5$ kJ/mol
Remarks:	liquid phase; solvent:solution
Conclusions	The material is predicted to readily undergo hydrolysis.
Reference	E.B. Lopatin, *et al., Kinetic and thermochemical characteristics of diketene-based reactions,* Khim.-Farm. Zh., 1992; **26**: 76-78.

Test Substance	
Test Substance:	Diketene
Remarks:	Purity unknown
Method	
Method:	Experimental
Test type:	Automatic Recording pH Titration
GLP:	No
Year:	1966
Results	
Nominal value:	Hydrolysis Rate Constant, $k = 120\ min^{-1}\ X10^3$ (25°C)
Remarks:	liquid phase; automatic addition of standardized base via capillary burette with instrument set to maintain constant pH of 7.0.
Conclusions	Diketene, which is the anhydride of acetoacetic acid, was determined to hydrolyze extremely rapidly in water.
Reference	B. L. Van Duuren and B.M. Goldschmidt., Carcinogenicity of Epoxides, Lactones and Peroxy Compounds. III. Biological and Chemical Reactivity, J Med Chem, 1966; **9**: 77-79.

C. Biodegradation

Test Substance	
Test Substance:	Diketene
Remarks:	Purity unknown
Method	
Method:	Modified MITI Test, OECD:TG-301C
Test type:	Ready biodegradability: Modified MITI Test (I)
GLP:	Yes
Year:	1992
Contact time:	28 days
Inoculum:	Activated sludge
Remarks:	300ml of test solution with a concentration of 100 mg/l of test substance was cultivated at 25°C for 28 days with a concentration of 30 mg/l of activated sludge.
Results	
Results:	
Degradation %:	95-102%
Time for 10% degradation:	Not noted
Classification:	Material determined to be readily biodegradable under the definition of the test.
Breakdown products:	Not determined
Remarks:	
Conclusions	Results indicate material would not be persistent in the environment.
Reference	Chemicals Inspection and Testing Institute; Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan; Japan Chemical Industry Ecology – Toxicology and Information Center, ISBN 4-89074-101-1; 1992.

D. Transport between Environmental Compartments (Fugacity)

Test Substance	
Test substance:	Diketene
Remarks:	
Method	
Test type:	Estimation
Model used:	Level III Fugacity Model; EPIWIN:EQC from Syracuse Research Corporation
Remarks:	Physical chemical values utilized in this model were -7.0 °C for MP, 127.4 °C for BP, and 10.7 mmHg for VP
Results	
Model data and results:	
Estimated distribution and media concentration (levels II/III):	Distribution (%) Air 3.65 Water 68.7 Soil 27.6 Sediment 0.115
Reference	Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPIWIN v 3.11) Syracuse Research Corporation, Syracuse, New York 13210. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay *et al.* 1996; *Environ. Toxicol. Chem.* **15(9)**, 1618-1626 and *Environ. Toxicol. Chem.* **15(9)**, 1627-1637.

IV. Ecotoxicity

A. Acute Toxicity to Fish

Test Substance	
Test Substance:	Diketene
Remarks:	Purity unknown
Method	
Method:	Other
Test type:	Acute toxicity to fish
GLP:	No (pre-GLP)
Year:	1978
Species/strain:	Golden Orfe (*Leucius idus melanotus*)
Analytical monitoring:	Not listed
Exposure duration:	Not listed
Remarks:	
Results	
Endpoint values:	LC_{50} = 150 mg/L
Data Quality	
Reliability:	Not assignable
Remarks:	
Reference	L. Goetsching et al., Pap.-Eucepa Symp., 1978, 389-408

Test Substance	
Test Substance:	Acetoacetic acid
Method	
Method:	Other: model calculation
Test type:	Acute toxicity to fish
GLP:	No
Year:	2003
Species/strain:	Fish/unknown
Exposure duration:	96 hours
Remarks:	Model compound class is neutral organics – acid. Physical-chemical inputs were default values.
Results	
Endpoint values:	EC_{50} = 479,000 mg/L
Data Quality	
Reliability:	Reliable with restriction
Remarks:	Modeled data
Reference	ECOSAR Program (v0.99); EPIWIN (v3.11)

B. Acute Toxicity to Aquatic Invertebrates

Test Substance	
Test Substance:	Acetoacetic acid
Method	
Method:	Other: model calculation
Test type:	Acute toxicity to Daphnid
GLP:	No
Year:	2003
Species/strain:	Daphnid
Exposure duration:	48 hours
Remarks:	Model compound class is neutral organics – acid. Physical-chemical inputs were default values.
Results	
Endpoint values:	EC_{50} = 418,000 mg/L
Data Quality	
Reliability:	Reliable with restriction
Remarks:	Modeled data
Reference	ECOSAR Program (v0.99); EPIWIN (v3.11)

C. Toxicity to Aquatic Plants

Test Substance	
Test Substance:	Acetoacetic acid
Method	
Method:	Other: model calculation
Test type:	Biomass
GLP:	No
Year:	2003
Species/strain:	Green algae
Exposure duration:	96 hours
Remarks:	Model compound class is neutral organics – acid. Physical-chemical inputs were default values.
Results	
Endpoint values:	EC_{50} = 220,000 mg/L
Data Quality	
Reliability:	Reliable with restriction
Remarks:	Modeled data
Reference	ECOSAR Program (v0.99); EPIWIN (v3.11)

V. Toxicological Data

A. Acute Toxicity

Test Substance	
Test Substance:	Ketene dimer
Remarks:	Purity unknown
Method	
Method:	Other
Test type:	Acute oral toxicity
GLP:	No (preGLP)
Year:	1974
Species/strain:	Rat/Carworth-Wistar
Sex:	Male
Animal/sex/dose:	5
Vehicle:	None indicated.
Route of exposure:	Oral (gavage)
Remarks:	Specific dose levels not listed
Results	
Value:	LD50 = 0.56 ml/kg
Deaths at each dose level:	Not indicated
Proper statistical evaluation used:	Yes, Thompson and Weil
Remarks:	
Conclusions	
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Significant amounts of study detail not published
References:	C. Carpenter *et al.*, Toxicol. Appl. Pharmacol., **28,** 313-319, 1974.

Test Substance	
Test Substance:	Diketene
Remarks:	Purity unknown
Method	
Method:	Other
Test type:	Acute toxicity
GLP:	No (preGLP)
Year:	1961
Species/strain:	Rat / unknown strain
Sex:	Unknown
Animals/Dose:	10 animals; Dose range 100 - 1600 mg/kg
Vehicle:	Corn oil
Route of exposure:	Oral gavage
Remarks:	Study lasted 14 days
Results	
Value:	LD_{50} = 400 – 800 mg/kg
Deaths at each dose level:	Unknown, deaths occurred between 4.5 hrs to 11 days
Proper statistical evaluation used:	Unknown
Remarks:	Rats were noted to be normal to very weak, rough coat, sides caved in, cyanosis, labored respiration, prostration

Conclusions	
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Significant amounts of study detail not published
References:	Laboratory of Industrial Medicine; Eastman Kodak Company; Rochester, NY; November 22, 1961.
Test Substance	
Test Substance:	Diketene
Remarks:	Purity unknown
Method	
Method:	Other
Test type:	Acute toxicity
GLP:	No (preGLP)
Year:	1961
Species/strain:	Mouse / unknown strain
Sex:	Unknown
Animals/dose:	20 animals; Dose range 100 - 3200 mg/kg
Vehicle:	Corn oil
Route of exposure:	Oral gavage
Remarks:	Study lasted 14-days
Results	
Value:	LD50 = 800 - 1600 mg/kg
Deaths at each dose level:	Unknown, deaths occurred between 0.75 to 1 day
Proper statistical evaluation used:	Unknown
Remarks:	Mice were noted to be normal to very weak, rough coat, sides caved in, diarrhea in high doses, tremor prostration
Conclusions	
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Significant amounts of study detail not published
References:	Laboratory of Industrial Medicine; Eastman Kodak Company; Rochester, NY; November 22, 1961.
Test Substance	
Test Substance:	Diketene
Remarks:	Purity unknown
Method	
Method:	Other: NAS-NRC - Principles and Procedures for Evaluating the Toxicity of Household Substances, Pub 1138, 1964.
Test type:	Acute oral toxicity
GLP:	No (preGLP)
Year:	1967
Species/strain:	Rat
Sex:	Unknown
Animal/sex/dose:	Unknown

Vehicle:	None indicated
Route of exposure:	Oral
Remarks:	Specific dose levels not listed
Results	
Value:	LD_{50} = 0.54 g/kg
Deaths at each dose level:	Not indicated.
Proper statistical evaluation used:	Unknown
Remarks:	
Conclusions	
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Significant amounts of study detail not published
References:	W.E. Rhinehart *et al.*, Indust. Hyg, Found. Of Amer., Chemical and Toxicological Series, Bulletin, **6**, 1-11, 1967.
Test Substance	
Test Substance:	Diketene
Remarks:	Purity: Unknown
Method	
Method:	Other
Test type:	Acute dermal toxicity
GLP:	No
Year:	1967
Species/strain:	Rabbit
Sex:	Not listed.
Animal/sex/dose:	Not listed
Vehicle:	None indicated
Route of exposure:	Dermal
Remarks:	
Results	
Value:	LD_{50} = 6.73 g/kg
Deaths at each dose level:	Not indicated.
Proper statistical evaluation used:	Yes
Remarks:	
Conclusions	
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Significant amounts of study detail not published
References:	W.E. Rhinehart et al, Indust. Hyg, Found. Of Amer., Chemical and Toxicological Series, Bulletin, **6**, 1-11,1967.

Test Substance	
Test Substance:	Ketene dimer
Remarks:	Purity unknown
Method	
Method:	Other
Test type:	Acute dermal toxicity
GLP:	No
Year:	1974
Species/strain:	Rabbit
Sex:	Not listed
Animal/sex/dose:	Not listed
Vehicle:	None indicated.
Route of exposure:	Dermal
Remarks:	
Results	
Value:	LD50 = 2.83 ml/kg
Deaths at each dose level:	Unknown
Proper statistical evaluation used:	Yes, Thompson and Weil
Remarks:	
Conclusions	
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Significant amounts of study detail not published
References:	C. Carpenter et al., Toxicol. Appl. Pharmacol., 28, 313-319, 1974.

Test Substance	
Test Substance:	Diketene
Remarks:	Purity unknown
Method	
Method:	Other
Test type:	Acute toxicity
GLP:	Yes
Year:	1987
Species/strain:	Rat / COBS CD(SD)BR
Sex:	Male and Female
Animal/sex/dose:	5/sex/dose; vapor concentration range 250, 500, 750 ppm
Route of exposure:	Inhalation; 1 hour
Remarks:	Study lasted 14-days and evaluated toxicity after 1 hour of exposure to diketene in vapor form. Vapors were generated by metering test material into a heated glass bead column. Animals were exposed in a 420L stainless steel and glass inhalation chamber. Temperature and relative humidity were 69-73 °F and 56-65% respectively. Animals were monitored for 14 days post exposure. Animals (approx. 8 weeks old) weighed 201-214 g (males) and 210-234 (females) at study initiation
Results	
Value:	LD_{10} = 346 ppm (males); 410 ppm (females); 370 ppm (both sexes)
Deaths at each dose level:	Deaths were seen at 250 ppm in either sex. At 500 ppm, two males and one female died on Day 1. At 750 ppm one male and two females died on Day 1. On Day 2, two males and one female died. One of each sex died on Day 6.
Remarks:	Weight gains were initially slow until Day 7 but ultimately all dose groups had positive gains at termination. Clinical signs of respiratory, eye irritation, and dyspnea were noted at all levels. No compound-related gross pathology was seen in animals found dead or in those surviving until Day 14.
Proper statistical evaluation used:	Probit analysis
Conclusions	
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented study conducted under GLP assurances
References:	Acute inhalation toxicity and one-hour LC10 value of diketene in the rat. Health and Environmental Laboratories; Eastman Kodak Company; Rochester, NY; HAEL No.: 85-0085; February 4, 1987.

B. Repeated Dose Toxicity

Please refer to data submitted to the US EPA HPV program on methyl acetoacetate (CAS No.: 105-45-3) and to data submitted to the US EPA as part of the OECD SIDS program on ethyl acetoacetate (CAS No.: 141-97-9).

Test Substance	
Test Substance:	Diketene
Remarks:	Purity: Not listed
Method	
Method:	Other
Test type:	Life-time dermal carcinogenicity study
GLP:	No
Year:	1967
Species/strain:	mouse/Swiss
Route of exposure:	3 X weekly Dermal application
Duration of test:	493/529-days
Dose level(s):	100 mg of 10% solution diketene in acetone and tricaprylin
Sex:	Female
Control group & treatment:	30 mice
Post-exposure observation period:	Not listed
Remarks:	
Results	
NOAEL:	100 mg of 10% solution
Toxic responses by dose:	Observations: Substance found to be inactive, no excess Tumors observed.
Proper statistical evaluation used:	Yes
Remarks:	
Conclusions	Material not found to be carcinogenic by dermal application in mice.
Data Quality	
Reliability:	Reliable with restriction.
Remarks:	
References:	B.L. van Duuren, *et al.*, Nat. Cancer Inst. **39**, 1217-1228, 1967.
Test Substance	
Test Substance:	Diketene
Remarks:	Purity: Not listed
Method	
Method:	Other
Test type:	Life-time subcutaneous carcinogenicity study
GLP:	No
Year:	1967
Species/strain:	Rat/Sprague-Dawley
Route of exposure:	1 X weekly Subcutaneous injection
Duration of test:	543-days
Dose level(s):	4 mg
Sex:	Not listed

Control group & treatment:	Not listed
Post-exposure observation period:	Not listed
Remarks:	
Results	
NOAEL:	4 mg
Toxic responses by dose:	Observations: Substance found to be inactive, no sarcomas observed.
Proper statistical evaluation used:	Yes
Remarks:	
Conclusions	Material not found to be carcinogenic by subcutaneous application in mice.
Data Quality	
Reliability:	Reliable with restriction.
Remarks:	
References:	B.L. van Duuren, *et al.*, Nat. Cancer Inst. **39,** 1213-1216, 1967.
Test Substance	
Test Substance:	Diketene
Remarks:	Purity: Not listed
Method	
Method:	Other
Test type:	Subcutaneous implantation carcinogenicity study
GLP:	No
Year:	1969
Species/strain:	Rat/Sprague-Dawley
Route of exposure:	Single subcutaneous implantation of gelatin capsule
Duration of test:	20-months
Dose level(s):	1.1 mg Diketene in 10 mg of trilaurin-tricaprylin (4:1)
Sex:	40 Female
Control group & treatment:	Not listed. Capsule implantation made in left axillary region.
Post-exposure observation period:	Not listed
Remarks:	Purpose of capsule implantation was to allow for slow seepage of the Diketene into the surrounding tissue.
Results	
NOAEL:	1.1 mg Diketene in 10 mg of trilaurin-tricaprylin (4:1)
Toxic responses by dose:	Observations: Substance found to be inactive, no local tumors observed.
Proper statistical evaluation used:	Yes
Remarks:	
Conclusions	No tumors were seen at site of implantation. Material was not found to be carcinogenic by subcutaneous implantation in rats.
Data Quality	
Reliability:	Reliable with restriction.
Remarks:	

References:	B.L. van Duuren., Carcinogenic epoxides, Lactones and Halo-ethers and their Mode of Action, Ann NY Acad Sci, 1969; **163**:633-651.

C. Genetic Toxicity – Mutation

Please refer to data submitted to the US EPA HPV program on methyl acetoacetate (CAS No.: 105-45-3) and to data submitted to the US EPA as part of the OECD SIDS program on ethyl acetoacetate (CAS No.: 141-97-9).

D. Genetic Toxicity – Chromosomal Aberrations

Please refer to data submitted to the US EPA HPV program on methyl acetoacetate (CAS No.: 105-45-3) and to data submitted to the US EPA as part of the OECD SIDS program on ethyl acetoacetate (CAS No.: 141-97-9).

E. Developmental Toxicity

Please refer to data submitted to the US EPA HPV program on methyl acetoacetate (CAS No.: 105-45-3) and to data submitted to the US EPA as part of the OECD SIDS program on ethyl acetoacetate (CAS No.: 141-97-9).

F. Reproductive Toxicity

Please refer to data submitted to the US EPA HPV program on methyl acetoacetate (CAS No.: 105-45-3) and to data submitted to the US EPA as part of the OECD SIDS program on ethyl acetoacetate (CAS No.: 141-97-9).